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The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to substantially reduce low-density lipoprotein cholesterol (LDL-C). Demonstrating whether efficacy and safety are maintained over a long duration of exposure is vital for clinical decision-making. The COMBO II trial compared the efficacy and safety of alirocumab versus ezetimibe over 2 years. A prespecified first analysis was reported at 52 weeks. Here we report the final end-of-study data (on-treatment) and evaluate post hoc the safety profile with longer versus shorter duration of alirocumab exposure. Patients (n = 720) on maximally tolerated statin dose were treated with alirocumab (75/150 mg every 2 weeks) or ezetimibe (10 mg/day). Overall mean adherence for both treatment groups during the first and second year was >97%. At 2 years, LDL-C was reduced by 49% (alirocumab) versus 17% (ezetimibe; p <0.0001), and LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients. Overall safety was similar in both treatment groups at 2 years and during the first versus the second year. Local injection-site reactions were reported by 2.5% (alirocumab) versus 0.8% (ezetimibe) during the first year, and 0.2% versus 0.5% during the second year, indicating early occurrence during prolonged alirocumab exposure. Two consecutive calculated LDL-C values <25 mg/dl were observed in 28% of alirocumab-treated patients (vs 0.4% with ezetimibe). Persistent anti-drug antibody responses were observed in 1.3% (6 of 454) of alirocumab-treated versus 0.4% (1 of 231) of ezetimibe-treated patients. Neutralizing antibodies (that inhibit binding in vitro) were observed in 1.5% (7 of 454) of alirocumab-treated patients (0 with ezetimibe), mostly at isolated time points. Alirocumab sustained substantial LDL-C reductions and was well tolerated up to 2 years in the COMBO II trial. **(Am J Cardiol 2017;■■:■■–■■)**

Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, reduces low-density lipoprotein cholesterol (LDL-C) levels by up to 61% in addition to statins ± lipid-lowering therapies.[1–3] The ODYSSEY Phase 3 COMBO II (NCT01644188) trial evaluated the efficacy and safety of alirocumab versus ezetimibe in reducing LDL-C in patients at high risk of cardiovascular (CV) events on maximally tolerated statin dose (MTD, defined in the supplement) who were not at pre-specified LDL-C target levels.[4,5] At 24 weeks, alirocumab reduced LDL-C by 51% (vs 21% with ezetimibe), corresponding to achieved LDL-C levels of 52 mg/dl and 83 mg/dl, respectively.[4] An important consideration is whether the number and nature of adverse events (AEs) change following long-term alirocumab exposure, considering the recent data on the variability in efficacy and AEs related to immunogenicity seen on treatment with bococizumab, another PCSK9 antibody.[6,7] Here we report the final end-of-study efficacy and safety data from the COMBO II trial to evaluate whether the effect of alirocumab versus ezetimibe is sustained for up to 2 years. We also compared post hoc the treatment adherence, safety, and the incidence of AEs in the first year versus the second year of the study.

Methods

Detailed methods and patient disposition have been reported previously (Figure 1).[4,5] Briefly, the multinational, multicenter, double-blind, active controlled, parallel-group study included patients with hypercholesterolemia and established coronary heart disease (CHD; defined in the Supplement) or CHD risk equivalents (ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥2 additional risk factors) not at National Cholesterol Education Program, Adult Treatment Panel III goal despite stable MTD for ≥4 weeks before the screening visit. The goal for patients with documented CV disease was LDL-C <70 mg/dl, or <100 mg/dl for patients without

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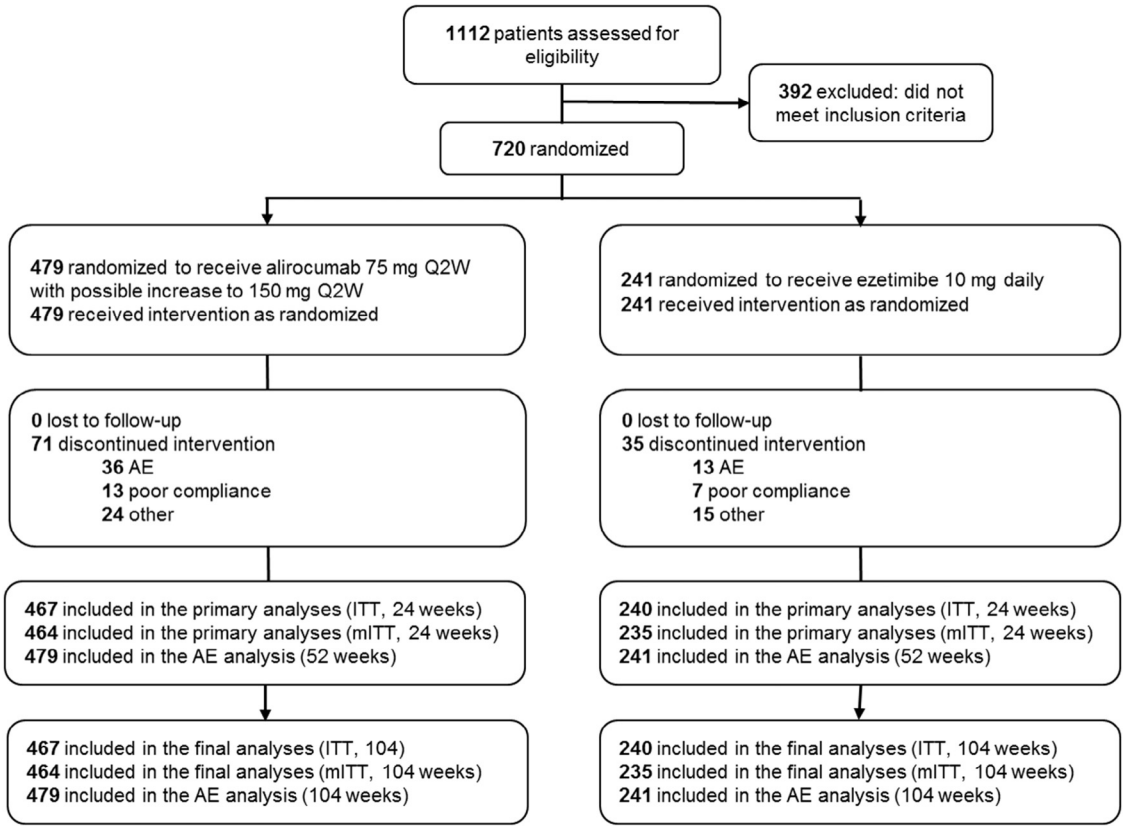

Figure 1. Consolidated Standards of Reporting Trials flow diagram. Patient disposition of the study population. AE = adverse event; ITT = intent to treat; mITT = modified intent to treat; Q2W = every 2 weeks.

a documented history of CV disease but at high CV risk. CV disease was defined as CHD, ischemic stroke, or peripheral artery disease.

Patients (n = 720) were randomized 2:1 to receive double-blind treatment for 2 years with either subcutaneous alirocumab 75 mg (in 1-ml volume) every 2 weeks (Q2W) (plus oral placebo for ezetimibe daily) or 10 mg oral ezetimibe daily (plus placebo subcutaneous Q2W for alirocumab) and continued to receive their background statin therapy. At week 12, the alirocumab dose was automatically increased to 150 mg Q2W (1-ml volume) if the week 8 LDL-C value was ≥70 mg/dl, while maintaining subject and investigator blinding. There was an 8-week posttreatment observation period following the 2-year (104-week) double-blind period. The protocol was approved by the institutional review boards of participating centers. All participants gave written informed consent. Race was self-reported in this study.

The primary end point was percentage change in calculated LDL-C from baseline to week 24, using all LDL-C values regardless of adherence to treatment (intent-to-treat [ITT] approach) and has been published previously.[4] Here, we report percentage change in calculated LDL-C from baseline up to 2 years by on-treatment analysis. For the on-treatment analysis, changes in lipoprotein values during the efficacy treatment period were assessed using the modified ITT population, defined as all randomized patients who received at least 1 dose or part of a dose of the double-blind study treatment and had an evaluable primary efficacy end point during the treatment period (defined as the period ending at last injection date + 21 days or last capsule administration date + 3 days, whichever comes first). The primary efficacy end point was evaluated when both baseline and at least 1 calculated LDL-C value on-treatment (during the efficacy period and within 1 of the analysis windows up to 2 years) were both available. Percentage changes in apolipoprotein (Apo) B, high-density lipoprotein cholesterol (HDL-C), lipoprotein(a) (Lp[a]), non–HDL-C, triglycerides, and Apo A1 from baseline to 2 years are also reported (on-treatment analysis).

The overall treatment adherence for injections was defined during the treatment period for each patient as follows: 100 − (percentage of days with below-planned dosing + percentage of days with above-planned dosing). Overall treatment adherence rates were analyzed in the first (weeks 0 to 52) and second (weeks 52 to 104) years of treatment (further details in the Supplement). Safety was assessed by analyzing AE reports and laboratory analyses from the time of signed informed consent until the end of the study. AEs were defined as treatment-emergent if they developed, worsened, or became serious during the period between first and last dose of study treatment (planned at week 102) plus 10 weeks (further details in the Supplement).

In addition to overall AE rates up to the end of the study, we also compared (post hoc) the rates of AEs in the first year (weeks 0 to 56) versus the second year (weeks 56 to 112) of the study. If a patient had an event once during weeks 0 to 56 and once during weeks 56 to 112, the 2 events were analyzed separately in the respective time period in which they occurred. Although the last treatment dose was at week 102,

residual effect of alirocumab is expected until 10 weeks after the last injection. The AE follow-up period is 8 weeks following the end-of-treatment visit at week 104; hence, the overall study period was up to 112 weeks. A comparison between weeks 0 to 56 and weeks 56 to 112 was used to allow for equal periods of treatment duration.

The presence of anti-drug antibodies (ADAs) was evaluated at weeks 0, 12, 24, 52, and 104 using a validated, titer-based immunoassay (sensitivity ~5 ng/ml; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; assay details in the Supplement and as reported previously[8]). A persistent ADA response was defined as 2 consecutive positive postbaseline responses separated by a minimum of 12 weeks. Samples positive for ADAs were further examined for neutralizing antibodies (NAbs), which are ADAs that inhibit the binding of alirocumab to PCSK9 in vitro (assay details in the Supplement and previously reported[8]).

All statistical analyses were performed by Sanofi at the direction of the independent investigators, who had access to any relevant data analysis on request in this study. Statistical analyses have been described previously.[4,5] A mixed-effect model with repeated measures was used to compare changes in LDL-C and other lipoproteins assumed to be normally distributed between alirocumab and ezetimibe patient groups over 2 years. Lipoproteins assumed to be non-normally distributed (i.e., triglycerides and Lp[a]) were analyzed using multiple imputation to handle missing data followed by robust regression model.

Results

Demographic characteristics, disease characteristics, and lipid parameters at baseline were generally similar in the alirocumab group compared with the ezetimibe group, and have been reported previously.[4] Mean (standard deviation [SD]) age at screening was 62 (9.3) years, 74% were male, and 85% were white. Mean (SD) baseline LDL-C levels were 109 (37) and 105 (34) mg/dl in the alirocumab (n = 479) and ezetimibe (n = 241) groups, respectively (Table S1 in the Supplement).

Atherosclerotic cardiovascular disease (ASCVD), which included CHD, ischemic stroke, and peripheral arterial disease, was documented in 95% of patients. Of the total population, 81% had hypertension and 31% had investigator-reported type 2 diabetes mellitus (defined by medical history, Table S1 in the Supplement).

Exposure to investigational medical product injections with ≥102 weeks' duration was observed in 79% (378 of 479) and 78% (187 of 241) of alirocumab- and ezetimibe-treated patients, respectively. Exposure to investigational medical product capsules with ≥102 weeks' duration was observed in 81% (381 of 472) and 79% (187 of 237) of alirocumab- and ezetimibe-treated patients, respectively.

The overall mean (SD) treatment adherence over 2 years was high in both groups: 98% (5.1) for the alirocumab-treated and 98% (3.5) for the ezetimibe-treated group. The majority of patients in the alirocumab (98%) and ezetimibe (99%) groups had at least 80% adherence for injections (i.e., patients received ≥80% of their injections on schedule). Similarly, 96% of alirocumab-treated and 98% of ezetimibe-treated patients had at least 80% adherence for capsules. There was no difference in treatment adherence between the first year and the second year of treatment. The overall mean (SD) treatment adherence for both treatment groups during the first and second year of treatment was >97%. The percentage of patients with ≥80% adherence for injections was 99% for both the alirocumab and the ezetimibe groups during the first year and 99% and 98%, respectively, during the second year. Similarly, the percentage of alirocumab-treated patients with ≥80% adherence for capsules was 97% (vs 99% ezetimibe-treated) during the first year and 97% (vs 98% ezetimibe-treated) during the second year.

In the on-treatment analysis, LDL-C was reduced from baseline to week 24 by 52% with alirocumab versus 22% with ezetimibe (least squares [LS] mean difference of −31%, 95% confidence interval [CI] −35 to −26; p <0.0001; Figure 2). A sustained effect of alirocumab was observed on calculated LDL-C over 2 years with reductions of 49% versus 17% with ezetimibe at 2 years (LS mean difference of −32%, 95% CI −38 to −26; p <0.0001; Figure 1, Table S2 in the Supplement). Alirocumab treatment for 2 years resulted in mean (standard error) calculated LDL-C values of 54 (1.8) mg/dl versus 87 (2.6) mg/dl on ezetimibe treatment (p <0.0001). LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients at 2 years.

Significant (p <0.0001) reductions from baseline up to 2 years were observed in Lp(a), Apo B, and non–HDL-C levels, whereas HDL-C levels significantly (p <0.0001) increased with alirocumab versus ezetimibe treatment (LS mean difference of +7.4% for percent change from baseline at 2 years, Figures 2). Triglycerides were reduced from baseline to 2 years by 8.2% in the alirocumab group and by 11.4% in the ezetimibe group, but the difference between treatment arms was not statistically significant (Figure 2).

Over the course of the whole study period, AEs were reported by 391 (82%) alirocumab-treated versus 198 (82%) ezetimibe-treated patients, and serious AEs were reported by 124 (26%) versus 60 (25%) patients, respectively. AEs leading to death occurred in 6 (1.3%) alirocumab-treated versus 6 (2.5%) ezetimibe-treated patients, and AEs leading to discontinuation of study treatment occurred in 44 (9.2%) versus 19 (7.9%) patients, respectively (Table 1).

In AEs of interest, higher rates were observed with alirocumab versus ezetimibe for injection-site reactions and allergic reactions (Table 1). Cataract conditions were observed in 10 (2.1%) alirocumab-treated and 6 (2.5%) ezetimibe-treated patients. Single elevations of alanine and aspartate aminotransferase were observed at higher frequencies with alirocumab versus ezetimibe, whereas creatinine kinase levels were comparable between the 2 groups (Table 1).

A comparison of AE rates between the first year and the second year of the study period identified local injection-site reactions in 12 (2.5%) alirocumab-treated versus 2 (0.8%) ezetimibe-treated patients during the first year, compared with 1 (0.2%) alirocumab-treated versus 1 (0.5%) ezetimibe-treated patient during the second year (Table 2). Of the 12 injection-site reactions reported by alirocumab-treated patients during the first year, 11 (92%) were of mild intensity (vs 2 [100%] in the ezetimibe group) and 1 (8.3%) was of moderate intensity (Table S3 in the Supplement). During the second year, the single (100%) injection-site reaction reported in the alirocumab group was of mild intensity (vs 1 [100%] of severe intensity in the ezetimibe group, Table S3 in the Supplement).

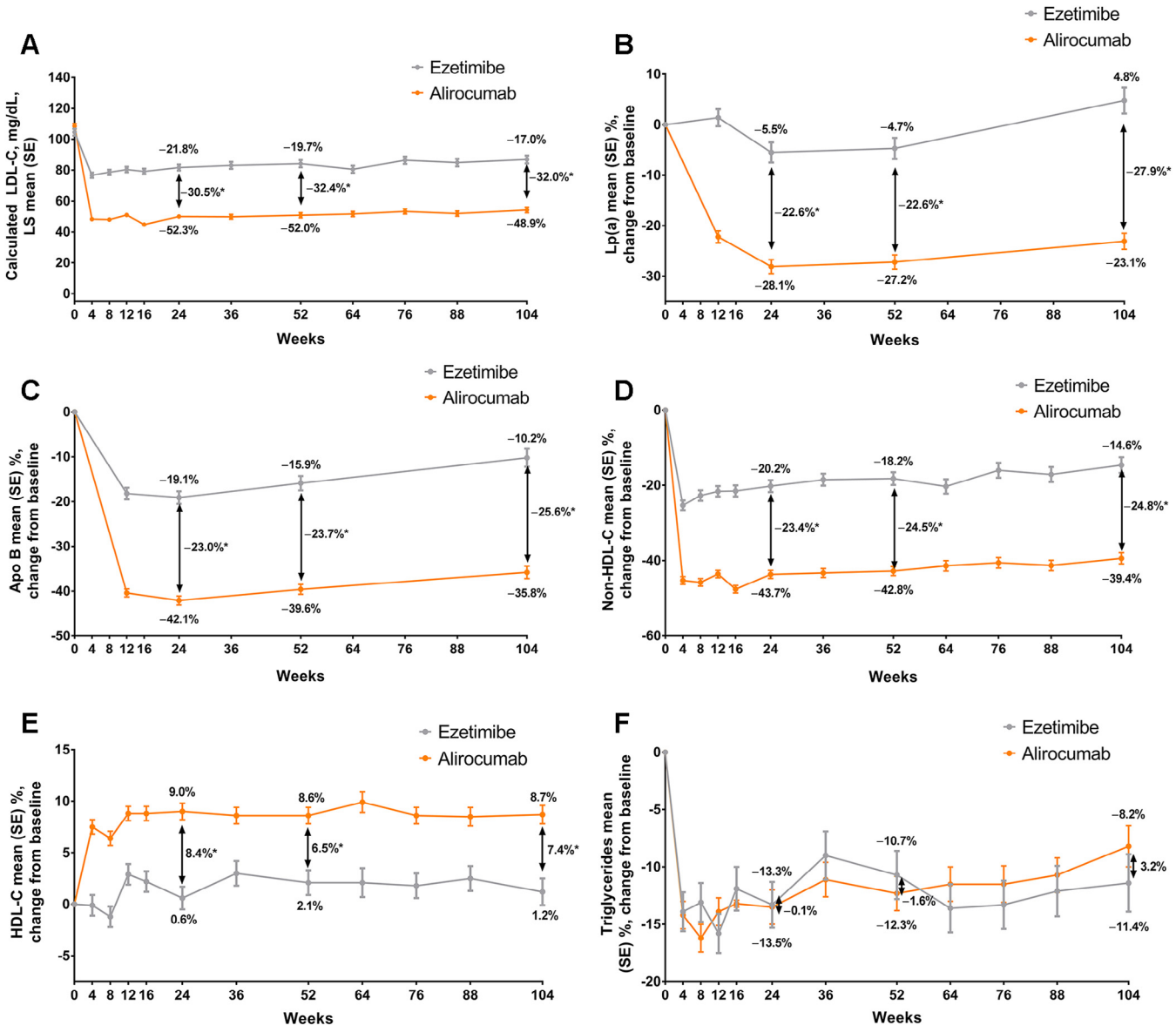

Figure 2. On-treatment analysis of (A) mean change in calculated LDL-C, and mean percent change from baseline in (B) Lp(a), (C) Apo B, (D) non–HDL-C, (E) HDL-C, and (F) triglycerides over 2 years. *p <0.0001 vs ezetimibe. Changes in lipoproteins versus study time points on treatment with alirocumab and ezetimibe. Values above and below the data points indicate the percentage reduction from baseline, with percentage differences indicated by the values next to the arrows. Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LS = least squares; SE = standard error.

Over the complete 2 years of follow-up, there was no meaningful difference between treatment groups over the study period for ophthalmological events, neurological or neurocognitive disorders, hepatic disorders, or AEs related to diabetes or diabetic complications (Table 1, Table S4 in the Supplement). Overall rates of specific AEs were similar in the alirocumab and ezetimibe groups for the first and the second year (Table 2). In other AEs of interest, rates were similar in the first and the second year of the study (Table 2).

At least 2 consecutive LDL-C values <25 mg/dl were observed in 128 (28%) patients in the alirocumab group (including 45 [9.8%] patients with 2 consecutive LDL-C values <15 mg/dl), of whom 91 (71%) reported at least 1 AE after the first LDL-C <25 mg/dl value (Table 3). The median time to the first calculated LDL-C value <25 mg/dl and <15 mg/dl was 12 and 16 weeks, respectively. Most patients were on 75 mg Q2W alirocumab at the time of the first LDL-C value <25 mg/dl (90%) and <15 mg/dl (88%). Of the 351 alirocumab-treated patients with LDL-C ≥25 mg/dl, 288 (82%) reported any AE (Table 3). The AE profile in patients with 2 consecutive LDL-C values <25 mg/dl was not notably different from the overall population or from patients with LDL-C ≥ 25 mg/dl, and no safety concerns were reported (Table 3). There were no injection-site reactions reported in these patients: 2 (1.6%) patients with 2 consecutive values of LDL-C <25 mg/dl versus 7 (2.0%) patients with LDL-C ≥25 mg/dl who reported cataracts. One ezetimibe-treated patient had 2 consecutive LDL-C <25 mg/dl values (time to the first value

Table 1
Frequency of adverse events from baseline to end of study (safety population)

Variable	Alirocumab (n = 479)	Ezetimibe (n = 241)
Any AE	391 (81.6%)	198 (82.2%)
Treatment–emergent SAE	124 (25.9%)	60 (24.9%)
AE leading to death	6 (1.3%)	6 (2.5%)
AE leading to permanent treatment discontinuation	44 (9.2%)	19 (7.9%)
AEs of special interest*		
Local injection-site reactions	13 (2.7%)	3 (1.2%)
General allergic reactions	38 (7.9%)	17 (7.1%)
Hemolytic anemia	0	0
Neurological events	19 (4.0%)	11 (4.6%)
Neurocognitive disorders	6 (1.3%)	5 (2.1%)
Ophthalmological events	9 (1.9%)	4 (1.7%)
Hepatic disorders	19 (4.0%)	11 (4.6%)
AEs related to diabetes mellitus or diabetic complications	35 (7.3%)	19 (7.9%)
Patients with diabetes at baseline	n = 148	n = 77
Any AE	17 (11.5%)	10 (13.0%)
Patients without diabetes at baseline	n = 331	n = 164
Any AE	18 (5.4%)	9 (5.5%)
MACE†	23 (4.8%)	8 (3.3%)
CHD death	4 (0.8%)	2 (0.8%)
Non-fatal MI	16 (3.3%)	5 (2.1%)
Ischemic stroke	2 (0.4%)	1 (0.4%)
Unstable angina requiring hospitalization	1 (0.2%)	1 (0.4%)
Ischemia driven coronary revascularization procedure‡	21 (4.4%)	7 (2.9%)
Laboratory parameters§		
Alanine aminotransferase >3 x ULN	10/470 (2.1%)	2/240 (0.8%)
Aspartate aminotransferase >3 x ULN	11/470 (2.3%)	1/240 (0.4%)
Creatine kinase >3 x ULN	17/467 (3.6%)	8/236 (3.4%)

n (%) = number and percentage of patients with at least 1 AE.

* Certain AEs were grouped as AEs of special interest (prespecified in the ODYSSEY phase 3 study protocols), based on identified, potential, and theoretical risks for the new drug class collected during the clinical trial program. AEs related to diabetes mellitus or diabetic complications are regardless of baseline status. Based on standard or custom Medical Dictionary of Regulatory Activities queries.

† Number and percentage of patients with at least 1 MACE (coronary heart disease death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization).

‡ Ischemia-driven coronary revascularization procedure related to coronary artery bypass grafting and percutaneous coronary intervention if the reason for procedure is new episode of ischemia occurring after randomization.

§ The denominator for each parameter within a treatment group is the number of patients who had that parameter assessed after baseline (not missing) during the AE period.

AE = adverse event; CHD = coronary heart disease; MACE = major adverse cardiac event; MI = myocardial infarction; SAE = serious adverse event; ULN = upper limit of normal.

of LDL-C < 25 mg/dl was 52 weeks); this patient did not report any AEs.

Persistent ADA responses were observed in 1.3% (6 of 454) of patients administered alirocumab versus 0.4% (1 of 231) of patients administered ezetimibe, with median time of onset being 12 and 52 weeks, respectively (Table S5). The first ADA response was observed in the first year (weeks 0 to 56) of treatment for all patients. ADA responses observed exhibited low titers, resolved over time, and had no clinical impact on either pharmacokinetics or safety of alirocumab. At least 1 NAb response was observed in 1.5% (7 of 454) of alirocumab-treated patients (mostly at single, isolated time points); no NAb responses were observed in ezetimibe-treated patients (Table S5). NAbs detected by immunoassays were transient and at isolated time points.

Discussion

These data indicate that the efficacy and safety of alirocumab are maintained through 2 years in high-risk patients when administered in addition to MTD at 75 mg Q2W, with potential increase to 150 mg Q2W based on individual LDL-C responses at week 8.

Overall treatment adherence was high in both treatment groups and did not vary between the first and the second year of the treatment period. In the on-treatment analysis, alirocumab resulted in sustained LDL-C reductions and goal achievement compared with ezetimibe, demonstrating superiority of treatment in patients at high CV risk not at LDL-C treatment goal. The slight decrease observed in efficacy at 2 years compared with efficacy at 24 weeks in the alirocumab-treated group was also observed in the ezetimibe-treated group.

The changes in atherogenic lipid levels observed in this study are consistent with those in the overall ODYSSEY trials.[9] Each LDL particle contains a molecule of Apo B. Uptake of LDL-C and other Apo B-containing lipids occurs via the LDL receptor. PCSK9 promotes degradation of the LDL receptor, hence alirocumab-mediated inhibition of PCSK9 increases LDL receptor availability resulting in reduced levels of not only LDL-C but also Apo B.[10] Non–HDL-C (total

Table 2
Frequency of adverse events in patients who received alirocumab versus ezetimibe reported at first (weeks 0 to 56) and second year (weeks 56 to 112)

Variable	Alirocumab		Ezetimibe	
	Weeks 0–56 (n = 479)	Weeks 56–112 (n = 411)	Weeks 0–56 (n = 241)	Weeks 56–112 (n = 209)
Any AE	343 (71.6%)	249 (60.6%)	166 (68.9%)	129 (61.7%)
Treatment–emergent SAE	87 (18.2%)	55 (13.4%)	40 (16.6%)	30 (14.4%)
AE leading to death	2 (0.4%)	4 (1.0%)	6 (2.5%)	2 (1.0%)
AE leading to permanent treatment discontinuation	39 (8.1%)	5 (1.2%)	15 (6.2%)	5 (2.4%)
AEs occurring in ≥5% of patients in any of the groups				
Infections and infestations	128 (26.7%)	75 (18.2%)	61 (25.3%)	67 (32.1%)
Upper respiratory tract infection	31 (6.5%)	14 (3.4%)	13 (5.4%)	6 (2.9%)
Musculoskeletal and connective tissue disorders	93 (19.4%)	64 (15.6%)	41 (17.0%)	25 (12.0%)
Myalgia	21 (4.4%)	6 (1.5%)	13 (5.4%)	0
Nervous system disorders	78 (16.3%)	39 (9.5%)	38 (15.8%)	24 (11.5%)
Dizziness	21 (4.4%)	9 (2.2%)	13 (5.4%)	6 (2.9%)
Gastrointestinal disorders	76 (15.9%)	37 (9.0%)	30 (12.4%)	31 (14.8%)
Injury, poisoning, and procedural complications	58 (12.1%)	46 (11.2%)	34 (14.1%)	20 (9.6%)
Accidental overdose	29 (6.1%)	22 (5.4%)	17 (7.1%)	5 (2.4%)
Cardiac disorders	58 (12.1%)	26 (6.3%)	28 (11.6%)	21 (10.0%)
General disorders and administration site conditions	56 (11.7%)	24 (5.8%)	25 (10.4%)	13 (6.2%)
Respiratory, thoracic, and mediastinal disorders	43 (9.0%)	20 (4.9%)	21 (8.7%)	16 (7.7%)
Investigations	38 (7.9%)	20 (4.9%)	23 (9.5%)	7 (3.3%)
Skin and subcutaneous tissue disorders	34 (7.1%)	19 (4.6%)	15 (6.2%)	4 (1.9%)
Vascular disorders	34 (7.1%)	27 (6.6%)	21 (8.7%)	14 (6.7%)
Metabolism and nutrition disorders	32 (6.7%)	19 (4.6%)	18 (7.5%)	10 (4.8%)
Psychiatric disorders	21 (4.4%)	9 (2.2%)	12 (5.0%)	4 (1.9%)
Eye disorders	21 (4.4%)	10 (2.4%)	6 (2.5%)	11 (5.3%)
Renal and urinary disorders	20 (4.2%)	17 (4.1%)	12 (5.0%)	8 (3.8%)
AEs of special interest*				
General allergic reaction	29 (6.1%)	13 (3.2%)	12 (5.0%)	5 (2.4%)
AEs related to diabetes mellitus or diabetic complications†	24 (5.0%)	13 (3.2%)	10 (4.1%)	9 (4.3%)
Neurological	13 (2.7%)	7 (1.7%)	6 (2.5%)	5 (2.4%)
Local injection-site reactions	12 (2.5%)	1 (0.2%)	2 (0.8%)	1 (0.5%)
Hepatic disorders	11 (2.3%)	9 (2.2%)	7 (2.9%)	6 (2.9%)
Ophthalmological	7 (1.5%)	2 (0.5%)	1 (0.4%)	3 (1.4%)
Neurocognitive disorder	3 (0.6%)	4 (1.0%)	4 (1.7%)	1 (0.5%)

Weeks 56 to 112 included double-blind treatment up to week 104 plus an 8-week follow-up. To have equal time periods for comparison, AEs were analyzed for weeks 0 to 56 and weeks 56 to 112. If a patient had an event once in weeks 0 to 56 and once in weeks 56 to 112, the 2 events were recorded separately in the respective time period they occurred.

* Certain AEs were grouped as AEs of special interest (prespecified in the phase 3 study protocols), based on identified, potential, and theoretical risks for the new drug class collected during the clinical trial program. These included local injection-site reactions, general allergic events, neurological events, hepatic disorders, and ophthalmological events. Other predefined categories, including AEs related to neurocognitive disorders and diabetes mellitus, were analyzed in the same way as the other AEs of interest, but not specifically defined as AEs of special interest in the protocols. AEs related to diabetes mellitus or diabetic complications are regardless of baseline status. Based on standard or custom Medical Dictionary of Regulatory Activities queries.

† AEs related to diabetes mellitus or diabetic complications are regardless of baseline status.

AE = adverse event; SAE = serious adverse event.

cholesterol minus HDL-C) is largely composed of LDL-C, and hence is also reduced with alirocumab. Studies also indicate that the increase in LDL receptors observed with alirocumab treatment may increase catabolism of Lp(a).[11,12] However, as statins reduce LDL-C but have little effect on Lp(a), other evidence suggests that Lp(a) reductions from PCSK9 inhibition may also be mediated by pathways not involving the LDL receptor.[13,14] An increase in HDL-C observed with alirocumab may be attributed to decreased LDL available to interact with cholesterol.[15,16]

Overall AEs at 2 years were mostly comparable between the 2 treatment groups, except for injection-site reactions and allergic reactions. Glycemic control over 2 years of treatment in all individuals with and without diabetes from COMBO II has been analyzed in a separate study.[17] Median fasting glucose and glycated hemoglobin values up to 2 years in those with and without diabetes were comparable between treatment groups.[17] The slightly increased rate of injection-site reactions in alirocumab-treated patients was seen only in the first year of the study, indicating that these reactions occur early during exposure. The decreased rate of injection-site reactions in the second compared with the first year was unlikely to be due to treatment discontinuation. The AE rates seen in patients with 2 consecutive calculated LDL-C values of <25 mg/dl were similar to the overall alirocumab-treated population.

Administration of alirocumab 75 mg Q2W or 75 mg increased to 150 mg Q2W as an add-on therapy over 2 years

Table 3
Frequency of adverse events in alirocumab-treated patients with 2 consecutive calculated low-density lipoprotein cholesterol values <25 mg/dl and with low-density lipoprotein cholesterol values ≥25 mg/dl (safety population)

Variable	Alirocumab 2 LDL-C < 25 mg/dL (n = 128)	Alirocumab LDL-C ≥ 25 mg/dL (n = 351)
Any AE	91 (71.1%)	288 (82.1%)
Treatment–emergent SAE	27 (21.1%)	92 (26.2%)
AE leading to death	0	6 (1.7%)
AE leading to permanent treatment discontinuation	6 (4.7%)	38 (10.8%)
AEs occurring in ≥5% of patients		
Infections and infestations	39 (30.5%)	124 (35.3%)
Nasopharyngitis	8 (6.3%)	11 (3.1%)
Upper respiratory tract infection	6 (4.7%)	34 (9.7%)
Musculoskeletal and connective tissue disorders	29 (22.7%)	107 (30.5%)
Arthralgia	5 (3.9%)	20 (5.7%)
Myalgia	4 (3.1%)	21 (6.0%)
Gastrointestinal disorders	25 (19.5%)	74 (21.1%)
Nervous system disorders	18 (14.1%)	84 (23.9%)
Dizziness	5 (3.9%)	23 (6.6%)
Headache	4 (3.1%)	25 (7.1%)
Cardiac disorders	16 (12.5%)	55 (15.7%)
Injury, poisoning, and procedural complications	15 (11.7%)	77 (21.9%)
Accidental overdose	8 (6.3%)	36 (10.3%)
Investigations	14 (10.9%)	38 (10.8%)
Metabolism and nutrition disorders	11 (8.6%)	34 (9.7%)
Diabetes mellitus	3 (2.3%)	7 (2.0%)
General disorders and administration site conditions	11 (8.6%)	55 (15.7%)
Skin and subcutaneous tissue disorders	11 (8.6%)	30 (8.5%)
Vascular disorders	10 (7.8%)	44 (12.5%)
Hypertension	6 (4.7%)	25 (7.1%)
Respiratory, thoracic, and mediastinal disorders	10 (7.8%)	45 (12.8%)
Renal and urinary disorders	9 (7.0%)	24 (6.8%)
Reproductive system and breast disorders	5 (3.9%)	18 (5.1%)
Psychiatric disorders	5 (3.9%)	23 (6.6%)
Eye disorders	3 (2.3%)	27 (7.7%)

n (%) = number and percentage of patients with at least 1 AE.

Only AEs that occurred, worsened, or became serious the day or after the first of the 2 consecutive LDL-C < 25 mg/dl are considered for alirocumab 2 LDL-C < 25 mg/dl group. Values are considered consecutive if spaced out by at least 21 days.

Alirocumab LDL-C ≥ 25 mg/dl group: alirocumab patients without 2 consecutive LDL-C < 25 mg/dl.

AE = adverse event; LDL-C = low-density lipoprotein cholesterol; SAE = serious adverse event.

was associated with low levels of immunogenicity. NAb responses identified by immunoassays were transient and observed in 7 alirocumab-treated patients. These responses do not necessarily impact clinical efficacy; however, a robust analysis of the efficacy of alirocumab by ADA status in this study was not possible because of the low patient numbers. In a pooled analysis of 10 ODYSSEY Phase 3 trials with 4747 patients, including the COMBO II study, ADA and NAb responses occurred at a low rate and were transient, occurring at single time points.[8] In the overall ODYSSEY program, mean reductions in LDL-C were maintained over time in patients with persistent and NAb responses.[8] Overall, the results of the post hoc safety analysis up to 2 years reported here are comparable with those reported previously up to 1.5 years (78 weeks) in the ODYSSEY LONG TERM study.[1] The similar safety profile of alirocumab- and ezetimibe-treated patients in the later time period of the study should be interpreted cautiously, as patients with AEs reported in the first year may have discontinued treatment. This study was not powered for analysis of CV events. Pooled post hoc analysis from the ODYSSEY program indicated a 24% risk reduction in major adverse CV events per 39 mg/dl lower LDL-C level (hazard ratio 0.79, 95% CI 0.63 to 0.91).[18] In this study, LDL-C was reduced by 53 mg/dl with alirocumab at 2 years. Recent clinical outcomes results with other PCSK9 inhibitors have yielded promising results.[6,19] The ongoing ODYSSEY OUTCOMES study has randomized approximately 18,000 patients to alirocumab or placebo to evaluate the effect of treatment on major adverse CV events.[20] These end-of-study data from COMBO II provide important information for clinicians and patients on the efficacy and safety of alirocumab co-administered with MTD.

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Supplementary Data

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